Comparison of potential risk factors for medication errors with and without patient harm

Zaal, Rianne J.; van Doormaal, J.E.; Lenderink, A.W.; Mol, P.G.M.; Kosterink, J.G.W.; Egberts, T.C.G.; Haaijer-Ruskamp, F.M.; van den Bemt, P.M.L.A.

Published in:
Pharmacoepidemiology and Drug Safety

DOI:
10.1002/pds.1977

PHARMACOEPIDEMIOLOGY AND DRUG SAFETY 2010; **19**: 825–833
Published online 7 June 2010 in Wiley InterScience (www.interscience.wiley.com) **DOI**: 10.1002/pds.1977

ORIGINAL REPORT

Comparison of potential risk factors for medication errors with and without patient harm

Rianne J. Zaal[1]*, Jasperien E. van Doormaal[2], Albert W. Lenderink[3], Peter G. M. Mol[4], Jos G.W. Kosterink[2], Toine C. G. Egberts[5,6], Flora M. Haaijer-Ruskamp[4] and Patricia M. L. A. van den Bemt[5,7]

[1]*Department of Clinical Pharmacy, TweeSteden hospital and St. Elisabeth Hospital, Tilburg, the Netherlands*
[2]*Department of Hospital and Clinical Pharmacy, University of Groningen and University Medical Center Groningen, Groningen, the Netherlands*
[3]*All care 4 IT, Loon op Zand, the Netherlands*
[4]*Department of Clinical Pharmacology, University of Groningen and University Medical Center Groningen, Groningen, the Netherlands*
[5]*Utrecht Institute for Pharmaceutical Sciences (UIPS), Department of Pharmacoepidemiology and Pharmacotherapy, Faculty of Science, Utrecht University, Utrecht, The Netherlands*
[6]*Department of Clinical Pharmacy, University Medical Center Utrecht, Utrecht, the Netherlands*
[7]*Department of Hospital Pharmacy, Erasmus MC, Rotterdam, the Netherlands*

SUMMARY

Purpose To compare determinants for medication errors leading to patient harm with determinants for medication errors without patient harm.
Methods A two-way case-control design was used to identify determinants for medication errors without harm (substudy 1) and determinants for medication errors causing harm (substudy 2). Data of patients admitted to five internal medicine wards of two Dutch hospitals during 5 months were collected prospectively by chart review. Medication errors were detected and classified by two pharmacists. Consensus between five pharmacists was reached on the causal relationship between medication errors and patient harm. Data analysis was performed by multivariate logistic regression.
Results We included 7286 medication orders, of which 3315 without errors (controls), and 5622 medication errors without harm (cases substudy 1) and 102 medication errors causing harm (cases substudy 2) were identified. Hospital, ward and the therapeutic class anti-infectives were associated with both medication errors without harm (hospital odds ratio (OR) 1.40; 95% confidence interval (CI) 1.21–1.63), TweeSteden hospital (TSh) geriatrics OR 2.03; 95% CI 1.73–2.38, TSh general internal medicine OR 1.44; 95% CI 1.23–1.69 and anti-infectives OR 1.28; 95% CI 1.06–1.56) and medication errors with harm (hospital OR 4.91; 95% CI 3.02–7.79, TSh geriatrics OR 5.76; 95% CI 2.52–13.15, TSh general internal medicine OR 6.51; 95% CI 2.82–15.02 and anti-infectives OR 4.20; 95% CI 2.24–7.90).
Conclusions This study shows that organisational determinants (hospital, ward) are comparable for medication errors with and without harm. For conclusions on patient- and medication-related determinants studies with larger sample sizes are needed. Copyright © 2010 John Wiley & Sons, Ltd.

KEY WORDS — medication errors; preventable adverse drug events; medication safety; hospitalised patients; determinants; pharmacoepidemiology

Received 28 July 2009; Revised 26 March 2010; Accepted 1 April 2010

INTRODUCTION

The prevalence of medication errors in hospitals is about 6% of all medication orders and approximately 10% of all medication errors is estimated to result in patient harm.[1] Whether or not a medication error results in patient harm depends on whether the error reaches the patient and when it does, on the intrinsic toxicity of the drug and the susceptibility of the patient to adverse events. Also, certain types of medication errors are more likely to cause patient harm than others, e.g. therapeutic prescribing errors result in harm more often than administrative prescribing errors do.[2–5]

Despite the fact that not all medication errors lead to patient harm, the impact of the problem of adverse drug events (ADEs) induced by such errors is rather large. The report 'To err is human' showed that in the United States 2% of all admitted patients is harmed as a result of a medication error and that 7000 patients die from medication errors annually.[6] This report has led to a

* Correspondence to: R. J. Zaal, Department of clinical pharmacy, TweeSteden hospital, PO Box 90 107, 5000 LA Tilburg, The Netherlands.
E-mail: rzaal@tsz.nl

renewed interest of health care professionals in improving medication safety. Such improvements can be achieved by effective interventions targeted at identified risk factors that contribute to unsafe practices and potential patient harm.

Whereas preventing actual patient harm is the ultimate goal of such medication safety initiatives, medication errors are often used as a surrogate outcome measure, because these occur more frequently and are easier to detect. However, the validity of this surrogate end point has not been established and it is unknown whether the risk factors associated with medication errors causing patient harm are the same as the risk factors associated with medication errors that do not cause harm. Therefore, we performed a study to compare the determinants for medication errors resulting in patient harm and the determinants for medication errors not resulting in harm.

METHODS

Design and setting

The design of the current study is a two-way case-control study. In a first substudy (first way), medication orders with errors not leading to patient harm (cases) were compared to medication orders without errors (controls). This first substudy aimed to identify determinants for medication errors not leading to patient harm. In the second substudy (second way) medication orders with errors leading to patient harm (cases) were again compared to the same medication orders without errors (controls) to identify determinants for medication errors leading to patient harm. Subsequently, determinants that were identified in the first substudy were compared with determinants identified in the second substudy.

This study is a part of the Physician Order Entry and Medication Safety (POEMS) study on the effect of a computerised physician order entry (CPOE) system on Medication Safety and associated costs.[5,7,8] The POEMS study is a prospective intervention study, performed in two medical wards (one geriatric and one general internal medicine ward) of the 600 bed teaching hospital 'TweeSteden' (TSh) in Tilburg and Waalwijk and three medical wards (two general internal medicine wards and one gastroenterology/rheumatology ward) of the 1300 bed University Medical Center in Groningen (UMCG), the Netherlands. The current study uses data of the period before the introduction of the CPOE system. The process of medication ordering and administration consisted of a hand-written system: physicians prescribed medication orders on charts and nurses transcribed these medication orders on administration charts. Therefore, clinical decision support could not be provided to physicians at the time of prescribing medication.

Patients

From July through November 2005 all patients admitted to the study wards for more than 24 hours were included. Patients received written information about the study after which they could object to inclusion. A waiver of the Medical Ethical Committee was obtained for this study, as the study fell within the boundaries of normal hospital care and routine of quality improvement and assurance.

Data collection

During ward visits the investigators prospectively extracted patients' characteristics (age, sex, weight and length) and data on diseases (medical history, reasons for admission and diagnoses) and adverse events (i.e. untoward medical occurrences which do not have to have a causal relationship with the treatment[9]) from medical records. Medication orders issued during hospitalisation were collected by reviewing medication order charts and administration charts. For ethical reasons, the physician was informed in case of potentially life threatening errors that were discovered during the process of data collection. These errors were not excluded from the study.

Classification of prescribing and transcribing errors

Medication errors were identified and categorised by two pharmacists according to the classification scheme for medication errors developed by the Dutch Association of Hospital Pharmacists.[10] During a pilot phase in the UMCG, two pharmacists were trained together to extract and classify medication errors uniformly. The classification distinguishes prescribing, transcribing, dispensing, administering and 'across settings' errors. In this study only prescribing and transcribing errors were recorded. Prescribing errors are subdivided into administrative errors (errors on readability, patient data, ward and prescriber data, drug name, dosage form and route of administration), dosing errors (errors on strength, frequency, dosage, length of therapy and directions for use) and therapeutic errors (interactions, contra-indications, incorrect monotherapy, duplicate therapy and errors on therapeutic drug monitoring or laboratory monitoring). Inappropri-

DOI: 10.1002/pds

ate drug choices were not actively assessed and were only taken into account when they were obvious. Transcribing errors are defined as errors in the process of interpreting, verifying and transcribing medication errors. The severity of all medication errors was assessed according to the index of the National Coordinating Council for Medication Error Reporting and Preventing (NCC MERP), which categorises medication errors into nine categories (A–I) based on severity of related patient outcomes (Table 1).[11] In this study, medication errors were divided into errors that did not lead to patient harm (NCC MERP category B up to D) and errors that did lead to harm (NCC MERP category E up to I).

Patient harm

Patient harm was defined as a preventable adverse drug event (pADE) which is an adverse drug event (ADE) that occurred due to a medication error with a possible or probable causal relationship with the medication error. To assess this relationship an algorithm was developed, based on the NCC MERP index and the Yale algorithm.[7,11,12] Our combined algorithm was described in detail and validated in a previous publication.[7] The Yale algorithm (Table 2) assesses the causality of the association between a drug and an adverse event. In our algorithm the first three items of the Yale algorithm were used: knowledge about the relation between the drug and the event, the presence of underlying clinical conditions which could be responsible for the event and the timing of the event. The causal relations between all medication errors made and the adverse events extracted from the medical records were assessed by five pharmacists. After individual assessment, consensus was reached for all cases on both causality and severity. The causal relationship could be defined as unlikely (score < 0), possible (score ≥ 0 and ≤ 3) or probable (score $= 4$). An event was defined as patient harm when consensus was reached on a possible or probable relationship with the medication error. Earlier we described the interobserver reliability on the presence of a preventable ADE and the severity of the preventable ADE assessed with the combined algorithm.[7]

Determinants

Determinants for medication errors or (preventable) ADEs that were identified in previous studies were included, provided that the data could be extracted from medical records or medication orders.[1–4,13–23] Potential determinants of medication errors with and without patient harm that were studied were organisational characteristics (hospital, ward, transfer from another hospital ward or care institution, length of stay and readmission to study ward during study period), patient characteristics (gender, age, renal impairment (defined as creatinine clearance $\leq$50 ml/minute during hospitalisation) and the number of medication orders per patient during hospital stay), characteristics of the medication order (weekday of prescription, dosage frequency less than once daily and route of administration) and the therapeutic area of the medication (identified by Anatomical-Therapeutic-Chemical (ATC) code).

Data analysis

All data were processed with MS Access 2003 and analysed with SPSS version 16.0.

Determinants for medication errors that did not lead to patient harm were identified by comparing medication orders containing these errors with medication orders without errors (substudy 1). Determinants for medication errors that resulted in patient harm were identified by comparing medication orders containing these errors with medication orders without errors (substudy 2). Univariate logistic regression analysis was performed with the medication order as

Table 1. NCC MERP categories

Category		Content
A	No harm	Circumstances or events that have the capacity to cause error
B		An error occurred but the error did not reach the patient
C		An error occurred that reached the patient but did not cause patient harm
D		An error occurred that reached the patient and required monitoring to confirm that it resulted in no harm to the patient and/or required intervention to preclude harm
E	Patient harm	An error occurred that may have contributed to or resulted in temporary harm to the patient and required intervention
F		An error occurred that may have contributed to or resulted in temporary harm to the patient and required initial or prolonged hospitalisation
G		An error occurred that may have contributed to or resulted in permanent patient harm
H		An error occurred that required intervention necessary to sustain life
I		An error occurred that may have contributed to or resulted in the patient's death

DOI: 10.1002/pds

Table 2. Simplified Yale algorithm[12]

	+1	0	−1
Axis 1	Adverse event is well accepted as ADR to suspected drug.	Adverse event is not well known or drug is new.	Adverse event previously unreported as ADR to well-known drug.
Axis 2	(a) No good alternative candidate (score +2) (b) Otherwise unexplained exacerbation or recurrence of underlying illness (score +1)	Alternative candidate(s) exist, but no good ones.	Good alternative candidate.
Axis 3	Timing as expected for ADR for this adverse event-drug pair.	Timing equivocal or non-assessable	Timing inconsistent for ADR for this adverse event-drug pair (score −2)
Total score Score < 0: ADR is unlikely Score ≥ 0 and $\leq +3$: ADR is possible. Score $= 4$: ADR is probable			

Abbreviations: ADR, adverse drug reaction.

unit of analysis. Multiple errors could have been made in one medication order and analysis was performed for each medication error separately.

For determinants that were statistically significantly associated ($p < 0.05$) with errors in the univariate analysis, a multivariable logistic regression analysis was performed using a manual stepwise forward logistic regression model. Determinants were consecutively entered into the model and when they changed the β coefficient with at least 10%, their contribution was considered relevant and the determinant remained in the model. Crude and adjusted odds ratios (ORs) with 95% confidence intervals (CIs) were calculated. Determinants that were significantly associated with medication errors without harm in substudy 1 were compared to determinants for medication errors leading to patient harm identified in substudy 2.

RESULTS

During data collection 558 patients were included and four patients were excluded from the study due to objection to inclusion. Since 28 patients were re-admitted once and three patients were re-admitted twice, 592 admissions were included in the study. During these admissions, 7286 medication orders were prescribed of which 3315 contained no error (controls). In the other 3971 medication orders a total of 5724 medication errors were identified of which 5622 did not cause patient harm (cases substudy 1) and 102 resulted in patient harm (cases substudy 2) (Figure 1). Nine medication errors were considered serious enough to require an intervention by the investigators to preclude harm. These errors were classified as errors that did not result in patient harm, but which required interventions to preclude harm (NCC MERP category D).

Details of the univariate and multivariate analysis of organisational characteristics, patient characteristics, characteristics of the medication order and the therapeutic area are presented in Tables 3–6.

After multivariate analysis, the following determinants were significantly associated with medication errors without patient harm: hospital, ward, transfer of patient, length of hospital stay, number of medication orders per patient during hospital stay, weekday of the prescription, route of administration and the therapeutic classes cardiovascular tract, genitourinary system and hormonal system, hormonal systemic therapy, anti-infectives, musculoskeletal system, nervous system and respiratory tract.

Of these determinants the following were also statistically significantly associated with medication errors with harm: hospital, ward and therapeutic class anti-infectives.

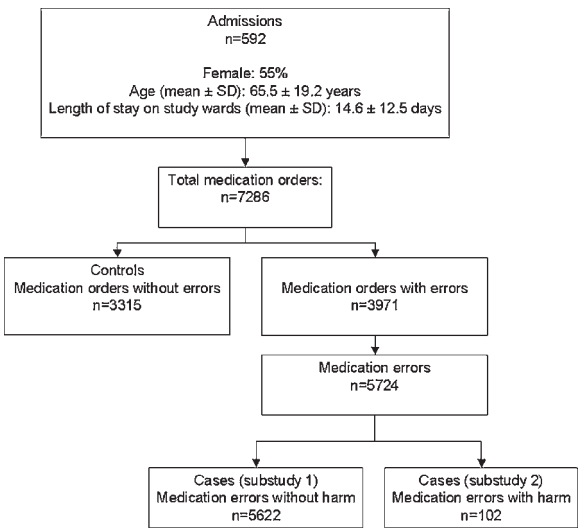

Figure 1. Patient characteristics, medication orders and medication errors

DOI: 10.1002/pds

Table 3. Organisational characteristics associated with medication errors with and without patient harm after univariate logistic regression (odds ratios) and multivariate logistic regression (adjusted odds ratios)

		Medication errors without harm (substudy 1)					Medication errors with harm (substudy 2)				
Potential determinant	Controls *n* (%)	Cases *n* (%)	OR	95% CI	OR_{adj}	95% CI	Cases *n* (%)	OR	95% CI	OR_{adj}	95% CI
Hospital											
TSh (UMCG is reference)	1459 (44.0)	3468 (61.7)	**2.05**	**1.88–2.24**	**1.40**[*]	**1.21–1.63**	81 (79.4)	**4.91**	**3.02–7.97**	**4.91**[†]	**3.02–7.97**
Ward											
UMCG general internal medicine	732 (22.1)	904 (16.1)	ref		ref		7 (6.9)	ref		ref	
UMCG gastroenterology/rheumatology	1124 (33.9)	1250 (22.2)	0.90	0.79–1.02	0.93[‡]	0.79–1.08	14 (13.7)	1.30	0.52–3.24	1.73[§]	0.68–4.41
TSh geriatrics	796 (24.0)	2250 (40.0)	**2.29**	**2.02–2.60**	**2.03**[‡]	**1.73–2.38**	49 (48.0)	**6.44**	**2.90–14.30**	**5.76**[§]	**2.52–13.15**
TSh general internal medicine	663 (20.0)	1218 (21.7)	**1.49**	**1.30–1.70**	**1.44**[‡]	**1.23–1.69**	32 (31.4)	**5.05**	**2.21–11.51**	**6.51**[§]	**2.82–15.02**
Transfer from: ($n = 8255/n = 3056$)											
Home (ref)	1566 (52.7)	3175 (60.1)	ref		ref		56 (59.6)	ref			
Another hospital ward	254 (8.5)	446 (8.4)	0.87	0.73–1.02	**0.68**[¶]	**0.58–0.81**	9 (9.6)	0.99	0.48–2.02		
Care institution	1151 (38.7)	1663 (31.5)	**0.71**	**0.65–0.79**	**0.86**[¶]	**0.78–0.96**	29 (30.9)	0.71	0.45–1.11		
Length of stay (days, mean ± SD)[**]	19.2 ± 15.5	22.2 ± 17.0	**1.01**	**1.01–1.02**	**1.02**[‖]	**1.01–1.02**	20.4 ± 11.7	1.00	0.99–1.02		
Readmission	233 (7.0)	360 (6.4)	0.91	0.76–1.07			8 (7.8)	1.13	0.54–2.35		

Figures in bold are statistically significant
Abbreviations: OR, odds ratio; 95%CI, 95% confidence interval; OR_{adj}, adjusted odds ratio; TSh, TweeSteden hospital; UMCG, University Medical Center Groningen; ref, reference
[*]Ward, transfer and day of prescription contributed significantly to the model
[†]No confounding factors were identified
[‡]Transfer, length of stay, age group, renal impairment, number of medication orders, day of prescription, and pharmacotherapeutic area contributed significantly to the model
[§]Age and pharmacotherapeutic area contributed significantly to the model
[¶]Hospital, ward and length of stay contributed significantly to the model
[‖]Number of medication orders contributed significantly to the model.
[**]Analysed as a continuous variable

Table 4. Patient characteristics associated with medication errors with and without patient harm after univariate logistic regression (odds ratios) and multivariate logistic regression (adjusted odds ratios)

		Medication errors without harm (substudy 1)					Medication errors with harm (substudy 2)				
Potential determinant	Controls n (%)	Cases n (%)	OR	95% CI	OR_{adj}	95% CI	Cases n (%)	OR	95% CI	OR_{adj}	95% CI
Female gender (male is reference)	1780 (53.7)	2990 (53.2)	0.98	0.90–1.07			47 (46.1)	0.74	0.50–1.10		
Age (years, mean ± SD)[**]	67.1 ± 17.8	70.8 ± 16.8	**1.01**	**1.01–1.02**	1.00[*]	1.00–1.01	74.1 ± 14.8	**1.03**	**1.01–1.04**	1.01[†]	1.00–1.03
<50 years	605 (18.3)	778 (13.8)	ref		ref		9 (8.8)	ref		ref	
50 to 64 years	668 (20.2)	882 (15.7)	1.03	0.89–1.19	1.00[‡]	0.85–1.18	12 (11.8)	1.21	0.51–2.89	1.35[§]	0.56–3.26
65 to 79 years	1053 (31.8)	1859 (33.1)	**1.38**	**1.21–1.56**	0.99[‡]	0.84–1.17	38 (37.3)	**2.43**	**1.17–5.05**	1.77[§]	0.81–3.90
≥ 80 years	989 (29.8)	2103 (37.4)	**1.65**	**1.45–1.88**	1.02[‡]	0.85–1.23	43 (42.2)	**2.92**	**1.42–6.04**	1.74[§]	0.76–4.02
Renal impairment	1700 (51.3)	3176 (56.5)	**1.23**	**1.13–1.34**	1.03[¶]	0.92–1.16	61 (59.8)	1.41	0.95–2.11		
Number of medication orders (mean ± SD)[**]	18.2 ± 10.7	19.2 ± 17.0	**1.01**	**1.00–1.01**	**0.99**[‖]	**0.99–1.00**	18.3 ± 9.1	1.00	0.98–1.02		
Polypharmacy (>4)	3253 (98.1)[#]	5534 (98.4)	1.20	0.86–1.66			103 (99.0)[#]	1.99	0.27–14.52		

Figures in bold are statistically significant.
Abbreviations: OR, odds ratio; 95%CI, 95% confidence interval; OR_{adj}, adjusted odds ratio.
[*]Hospital, ward, length of stay and pharmacotherapeutic area contributed significantly to the model.
[†]Hospital contributed significantly to the model.
[‡]Hospital, ward, transfer, length of stay, renal impairment, number of medication orders, day of prescription, route of administration and pharmacotherapeutic area contributed significantly to the model.
[§]Hospital, ward and pharmacotherapeutic area contributed significantly to the model.
[¶]Hospital, ward, transfer, length of stay, age, number of medication orders, day of prescription, route of administration and pharmacotherapeutic area contributed significantly to the model.
[‖]Hospital, ward, transfer, length of stay, day of prescription, route of administration and pharmacotherapeutic area contributed significantly to the model.
[**]Analysed as a continuous variable.
[#]Dummy variables included.

DOI: 10.1002/pds

Table 5. Characteristics of the medication order associated with medication errors with and without patient harm after univariate logistic regression (odds ratios) and multivariate logistic regression (adjusted odds ratios)

		Medication errors without harm (substudy 1)					Medication errors with harm (substudy 2)				
Potential determinant	Controls *n* (%)	Cases *n* (%)	OR	95% CI	OR_{adj}	95% CI	Cases *n* (%)	OR	95% CI	OR_{adj}	95% CI
Day of prescription ($n = 8899/3398$)											
Monday	631 (19.1)	959 (17.1)	ref		ref		18 (17.8)	ref			
Tuesday	559 (17.0)	871 (15.5)	1.03	0.89–1.19	1.03*	0.88–1.20	15 (14.9)	0.94	0.47–1.88		
Wednesday	557 (16.9)	971 (17.3)	1.15	0.99–1.33	1.10*	0.94–1.27	21 (20.8)	1.32	0.70–2.51		
Thursday	530 (16.1)	951 (17.0)	**1.18**	**1.02–1.37**	1.08*	0.93–1.26	20 (19.8)	1.32	0.70–2.53		
Friday	587 (17.8)	1120 (20.0)	**1.26**	**1.09–1.45**	**1.22***	**1.05–1.41**	18 (17.8)	1.08	0.55–2.09		
Saturday	203 (6.2)	352 (6.3)	1.14	0.93–1.40	**1.28***	**1.04–1.57**	7 (6.9)	1.21	0.50–2.94		
Sunday	230 (7.0)	378 (6.7)	1.08	0.89–1.31	1.17*	0.96–1.43	2 (2.0)	0.31	0.07–1.32		
Weekend (weekdays are reference)	433 (13.1)	730 (13.0)	0.99	0.87–1.13			9 (8.9)	0.65	0.32–1.29		
Dosage frequency < once daily	84 (2.5)§	163 (2.9)	1.16	0.89–1.52			1 (1.0)§	0.37	0.05–2.71		
Route of administration											
Oral	2346 (70.8)	3701 (65.8)	ref		ref		72 (70.6)	ref			
Topical	35 (1.1)	94 (1.7)	**1.70**	**1.15–2.52**	2.13†	0.99–4.62	1 (1.0)	0.93	0.13–6.89		
Inhalation	66 (2.0)	209 (3.7)	**2.01**	**1.52–2.66**	1.17†	0.71–1.92	4 (3.9)	1.98	0.70–5.57		
Dermal	19 (0.6)	123 (2.2)	**4.10**	**2.52–6.67**	**3.31†**	**1.31–8.41**	0 (0)	‡			
Parenteral	758 (22.9)	1121 (19.9)	0.94	0.84–1.04	1.04†	0.91–1.18	23 (22.5)	0.99	0.61–1.59		
Rectal	62 (1.9)	280 (5.0)	**2.86**	**2.16–3.79**	**3.19†**	**2.33–4.37**	2 (2.0)	1.05	0.25–4.38		
Transdermal	29 (0.9)	55 (1.0)	1.20	0.76–1.89	0.91†	0.52–1.57	0 (0)	‡			
Sublingual	0 (0)	39 (0.7)	‡		‡		0 (0)	‡			

Figures in bold are statistically significant.
Abbreviations: OR, odds ratio; 95%CI, 95% confidence interval; OR_{adj}, adjusted odds ratio ref, reference.
*Hospital, ward, length of stay, route of administration and pharmacotherapeutic area contributed significantly to the model.
†Hospital, ward, transfer, length of stay, number of medication orders, day of prescription and pharmacotherapeutic area contributed significantly to the model.
‡Statistical analysis not possible due to insufficient data.
§Dummy variables included.

Table 6. Therapeutic areas associated with medication errors with and without patient harm after univariate logistic regression (odds ratios) and multivariate logistic regression (adjusted odds ratios)

		Medication errors without harm (substudy 1)					Medication errors with harm (substudy 2)				
Potential determinant	Controls n (%)	Cases n (%)	OR	95% CI	OR_{adj}	95% CI	Cases n (%)	OR	95% CI	OR_{adj}	95% CI
Therapeutic area (ATC-code)											
Gastrointestinal tract (A)	835 (25.2)	1166 (20.7)	ref		ref		20 (19.6)	ref		ref	
Blood system (B)	478 (14.4)	691 (12.3)	1.04	0.89–1.20	1.13*	0.95–1.33	14 (13.7)	1.22	0.61–2.44	1.22	0.60–2.45
Cardiovascular tract (C)	716 (21.6)	831 (14.8)	**0.83**	**0.73–0.95**	**0.82***	**0.71–0.94**	10 (9.8)	0.58	0.27–1.25	0.48	0.22–1.03
Dermatologicals (D)	24 (0.7)	124 (2.2)	**3.70**	**2.37–5.78**	1.45*	0.59–3.53	0 (0)	‡		‡	
Genitourinary system and sex hormones (G)	40 (1.2)	35 (0.6)	**0.63**	**0.40–1.00**	**0.59***	**0.36–0.96**	1 (1.0)	1.04	0.14–7.97	0.84	0.11–6.51
Hormonal systemic therapy (H)	126 (3.8)	249 (4.4)	**1.42**	**1.12–1.79**	**1.63***	**1.26–2.10**	1 (1.0)	0.33	0.04–2.49	0.37	0.05–2.77
Anti-infectives (J)	264 (8.0)	454 (8.1)	**1.23**	**1.03–1.47**	**1.28***	**1.06–1.56**	23 (22.5)	**3.64**	**1.97–6.73**	**4.20†**	**2.24–7.90**
Cancer therapy (L)	47 (1.4)	47 (0.8)	0.72	0.47–1.08	0.81*	0.49–1.35	0 (0)	‡		‡	
Musculo-skeletal system (M)	86 (2.6)	172 (3.1)	**1.43**	**1.09–1.89**	**1.62***	**1.20–2.20**	2 (2.0)	0.97	0.22–4.22	1.08	0.25–4.75
Nervous system (N)	537 (16.2)	1415 (25.2)	**1.89**	**1.65–2.16**	**1.85***	**1.60–2.14**	25 (24.5)	**1.94**	**1.07–3.53**	1.62†	0.89–2.98
Anti-parasitic products, insecticides and repellents (P)	13 (0.4)	5 (0.1)	**0.28**	**0.10–0.78**	0.40*	0.14–1.18	0 (0)	‡		‡	
Respiratory tract (R)	104 (3.1)	324 (5.8)	**2.23**	**1.76–2.83**	**2.30***	**1.54–3.43**	5 (4.9)	2.01	0.74–5.46	2.15	0.78–5.94
Sensory organs (S)	28 (0.8)	68 (1.2)	**1.74**	**1.11–2.73**	0.92*	0.38–2.21	1 (1.0)	1.49	0.19–11.51	1.56	0.19–12.50
Various (V)	13 (0.4)	36 (0.6)	**1.98**	**1.05–3.76**	1.11*	0.51–2.42	0 (0)	‡		‡	
Unknown	4 (0.1)	5 (0.1)	0.90	0.24–3.34	1.02*	0.23–4.59	0 (0)	‡		‡	

Figures in bold are statistically significant.
Abbreviations: OR, odds ratio; 95%CI, 95% confidence interval; OR_{adj}, adjusted odds ratio; ref, reference.
*Hospital, ward, transfer, length of stay, day of prescription and route of administration contributed significantly to the model.
†Hospital, ward and age contributed significantly to the model.
‡Statistical analysis not possible due to insufficient data.

DOI: 10.1002/pds

All other determinants that were statistically significantly associated with medication errors without harm (transfer of patient, length of hospital stay, number of medication orders per patient, day of prescription, route of administration and the other therapeutic classes) showed no association with medication errors with harm in the univariate analysis already, had insufficient cases per category to analyse the association or showed a different trend in the OR. No determinants for medication errors leading to harm were identified that had not been identified as determinant for medication errors without harm.

DISCUSSION

This study is the first study on the comparison of determinants for medication errors with and without consequent patient harm. Hospital, ward and the therapeutic class of anti-infectives were shown to be determinants for both types of medication errors.

In this study relatively few medication errors causing patient harm were identified, despite the collection of more than 7000 medication orders during 5 months of daily ward visits. This main limitation of our study may explain why many of the determinants that were identified in the multivariate analysis for medication errors without harm, were non-significant in the univariate analysis for medication errors with harm.

The determinants hospital and ward point in the same direction, namely that errors (either with or without harm) probably occur more often in the TSh than in the UMCG. Thus, even after correction for case-mix, it remains likely that the personnel or local processes influence the prevalence of errors, irrespective of the outcome.

Therefore, it may be concluded that for these organisational determinants, medication errors are an acceptable surrogate outcome measure for patient harm. This corresponds with findings of previous studies separately showing that organisational determinants are linked to respectively medication errors and pADEs.[2,4,14,16,19,21]

Differences between the two hospitals and wards might be explained by differences in training of the physicians.[1,16,19,21,24,25] The UMCG is a university tertiary care teaching hospital while the TSh is a secondary care teaching hospital, where less education may lead to more errors.

Due to the limited power of our study for medication errors leading to harm, definite conclusions on determinants that are more patient- or medication-related cannot be drawn, with the possible exception of anti-infectives. The association between anti-infectives and errors might be explained by the fact that choosing the right anti-infective for an infection could be more difficult than choosing drugs for other indications. Moreover, the dosage of most anti-infectives must be adjusted according to the patient's renal function, so dosage errors are made more easily. Theoretically, it seems likely that for medication errors leading to patient harm, specific determinants may be identified that reflect either the vulnerability of the patient to experience pADEs or the intrinsic toxicity of the medication. Anti-infectives, for example, have a great intrinsic toxicity and are prescribed to acutely ill patients, who are very susceptible for ADEs. This might explain the association between anti-infectives and pADEs.[1–3,14,17,19,22,23] Again, the determinants identified in our study for medication errors without harm were identified in other studies, both for medication errors (identified determinants were number of medication orders per patient, route of administration and pharmacotherapeutic area[1,18,20]) and for (preventable) ADEs (identified determinants were among others number of medication orders per patient and therapeutic area[1,14,17,19,20,22,23]). However, none of these previous studies compared the determinants for medication errors without harm with the determinants for medication errors leading to patient harm.

A number of explanations for identified associations between specific determinants and the risk of medication errors without harm can be given. First of all, transfer of patients from home was associated with medication errors without harm in this study. Because no medication reconciliation was performed at admission, errors can be made more easily when patients are admitted from home, compared to transfers between hospital wards or other affiliated care institutions when actual medication is exchanged in a specified way between health care professionals.

Prolonged length of stay increased the risk of a medication error without harm. In the handwritten system the medication orders have to be transcribed again by nurses on a new administration chart when an old chart is completed, which can cause transcribing errors, which may explain this increased risk of medication errors.

After correcting for confounding factors, an increasing number of medication orders decreases the risk of medication errors without harm slightly. This is not consistent with previous studies and can possibly be explained by extra attention of physicians to patients who use more drugs.[15] Medication orders prescribed on Friday and Saturday were at risk for medication errors without harm, which can be explained by a higher workload and less knowledge about the patient's

DOI: 10.1002/pds

condition, because of staff changes and fewer physicians being present.[4,16,19,21] With dermal preparations, directions for use, for example the site of application, were often missing on the prescription. This is an explanation for the high number of errors without harm.[18]

For all of the determinants that were associated with medication errors without harm, it can be suggested that most of these errors were administrative errors which result in patient harm less often than therapeutic errors.[5]

Although most of the determinants identified in this study cannot be influenced by health care professionals directly to prevent patient harm, they give a first impression of risk departments, risk processes and risk medication and they are suitable to provide an answer to the main study aim. However, future studies should also focus on determinants that are more likely to be influenced by health care professionals. Besides the small sample size of medication errors leading to harm, this study has several other limitations. First, only five wards in two hospitals were studied, so the results cannot be generalised to other medical specialties, wards or hospitals. Second, the medication ordering was done in the context of a handwritten system. Implementation of a CPOE system with clinical decision support could change the risk factors for medication errors. Third, risk factors for medication errors and consequent harm could differ between continuation of pre-admission treatment and hospital-initiated drugs. Because it was not necessary to define pre-admission treatment in the POEMS study and medication reconciliation was not performed, this determinant could not be included in this study either. However, prescribing errors and transcribing errors in medication orders for continuation of pre-admission treatment were assessed. Finally, only prescribing and transcribing errors were considered in this study. To provide a full overview of the potential determinants for medication errors with and without harm distribution errors, administration errors and 'across settings' errors should also be studied.

The main strength of this study is the epidemiological approach to identify risk factors by calculating ORs, whereas many other studies used error frequencies. Moreover, we established the actual outcome of the medication error instead of the potential harm an error could cause which many other studies did and our study is the first comparing determinants for medication errors without and with patient harm.

Future research with a larger sample size of medication errors leading to patient harm is recommended. These future studies should also take into account other types of medication errors and include more organisational determinants (such as the use of electronic prescribing) and patient related factors (like the reason for admission and comorbidities).

KEY POINTS

- Medication errors resulting in patient harm and medication errors without patient harm have some determinants in common.
- Common determinants were mainly at the organisational level.

CONCLUSION

To conclude, medication errors resulting in harm and medication errors without harm have some determinants in common, which are mainly at the organisational level. Therefore, the present study gives a first direction about the validity of medication errors as a surrogate outcome measure when looking at these organisational aspects. More determinants could possibly be identified in studies with larger sample sizes, which may identify specific patient- and medication-related determinants for medication errors leading to patient harm.

CONFLICTS OF INTEREST

Authors declare no conflict of interest.

ACKNOWLEDGEMENTS

This study was supported by a grant of The Netherlands Organization for Health Research and Development (ZonMw).

REFERENCES

1. Krähenbühl-Melcher A, Schlienger R, Lampert M, Haschke M, Drewe J, Krähenbühl S. Drug-related problems in hospitals: a review of the recent literature. *Drug Saf* 2007; **30**: 379–407.
2. Bates DW. Frequency, consequences and prevention of adverse drug events. *J Qual Clin Pract* 1999; **19**: 13–17.
3. Bates DW, Cullen DJ, Laird N, *et al*. Incidence of adverse drug events and potential adverse drug events. Implications for prevention. ADE Prevention Study Group. *JAMA* 1995; **274**: 29–34.
4. Leape LL, Bates DW, Cullen DJ, *et al*. Systems analysis of adverse drug events. ADE Prevention Study Group. *JAMA* 1995; **274**: 35–43.
5. van Doormaal JE, van den Bemt PMLA, Mol PGM, *et al*. Medication errors: the impact of prescribing and transcribing errors on preventable harm in hospitalised patients. *Qual Saf Health Care* 2009; **18**: 22–27.
6. Institute of Medicine. *To Err is Human: Building a Safer Health System*. National Academy Press: Washington DC, 2000; 312.
7. Van Doormaal JE, Mol PGM, Van den Bemt PMLA, *et al*. Reliability of the assessment of preventable adverse drug events in daily clinical practice. *Pharmacoepidemiol Drug Saf* 2008; **17**: 645–654.

8. van Doormaal JE, van den Bemt PMLA, Zaal RJ, *et al*. The influence that electronic prescribing has on medication errors and preventable adverse drug events: an interrupted time-series study. *J Am Med Inform Assoc* 2009; **16**: 816–825.
9. The Uppsala Monitoring Centre. Glossary of terms used in Pharmacovigilance. http://www.who-umc.org/graphics/15338.pdf
10. Van den Bemt PMLA, Egberts ACG. Drug-related problems: definitions and classifications. *EJHP Practice* 2007; **13**: 62–64.
11. National Coordinating Council for Medication Error Reporting and Preventing. NCC MERP index for categorizing medication errors. http://www.nccmerp.org/pdf/indexColor2001-06-12.pdf
12. Kramer MS, Leventhal JM, Hutchinson TA, Feinstein AR. An algorithm for the operational assessment of adverse drug reactions. Background, description, and instructions for use. *JAMA* 1979; **242**: 623–632.
13. Bates DW, Boyle DL, Van der Vliet MB, Schneider J, Leape L. Relationship between medication errors and adverse drug events. *J Gen Intern Med* 1995; **10**: 199–205.
14. Bates DW, Miller EB, Cullen DJ, *et al*. Patient risk factors for adverse drug events in hospitalized patients. ADE Prevention Study Group. *Arch Intern Med* 1999; **159**: 2553–2560.
15. Blix HS, Viktil KK, Reikvam A, *et al*. The majority of hospitalised patients have drug-related problems: results from a prospective study in general hospitals. *Eur J Clin Pharmacol* 2004; **60**: 651–658.
16. Dean B, Schachter M, Vincent C, Barber N. Causes of prescribing errors in hospital inpatients: a prospective study. *Lancet* 2002; **359**: 1373–1378.
17. Evans RS, Lloyd JF, Stoddard GJ, Nebeker JR, Samore MH. Risk factors for adverse drug events: a 10-year analysis. *Ann Pharmacother* 2005; **39**: 1161–1168.
18. Fijn R, Van den Bemt PMLA, Chow M, De Blaey CJ, De Jong-Van den Berg LT, Brouwers JR. Hospital prescribing errors: epidemiological assessment of predictors. *Br J Clin Pharmacol* 2002; **53**: 326–331.
19. Kanjanarat P, Winterstein AG, Johns TE, Hatton RC, Gonzales-Rothi R, Segal R. Nature of preventable adverse drug events in hospitals: a literature review. *Am J Health Syst Pharm* 2003; **60**: 1750–1759.
20. Leendertse AJ, Egberts ACG, Stoker LJ, van den Bemt PMLA. Frequency of and risk factors for preventable medication-related hospital admissions in the Netherlands. *Arch Intern Med* 2008; **168**: 1890–1896.
21. Lesar TS, Briceland L, Stein DS. Factors related to errors in medication prescribing. *JAMA* 1997; **277**: 312–317.
22. Van den Bemt PMLA, Egberts ACG, Lenderink AW, *et al*. Risk factors for the development of adverse drug events in hospitalized patients. *Pharm World Sci* 2000; **22**: 62–66.
23. Von Laue NC, Schwappach DL, Koeck CM. The epidemiology of preventable adverse drug events: a review of the literature. *Wien Klin Wochenschr* 2003; **115**: 407–415.
24. Lesar TS, Briceland LL, Delcoure K, Parmalee JC, Masta-Gornic V, Pohl H. Medication prescribing errors in a teaching hospital. *JAMA* 1990; **263**: 2329–2334.
25. Van den Bemt PMLA, Egberts TCG, De Jong-van den Berg LT, Brouwers JR. Drug-related problems in hospitalised patients. *Drug Saf* 2000; **22**: 321–333.

DOI: 10.1002/pds